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ORIGINAL RESEARCH ARTICLE

Impact of clinical pharmacists on adherence to stress ulcer prophylaxis protocol in critically ill Egyptian patients: a comparative study

Naglaa Samir Bazan[1,2] · **Samar Farghali Farid**[3] · **Darrin Lloyd Baines**[4]

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Abstract

Background Standardized protocols can aid in appropriate prescribing of stress ulcer prophylaxis (SUP) in the intensive care unit (ICU). The study aimed to evaluate the impact of providing a physician's education (PhyEd) versus a PhyEd + Clinical Pharmacist (PhyEd + CPh) approach on adherence to a SUP protocol and possible cost saving in the ICU.

Methods This was a quasi-experimental study. An evidence-based SUP protocol was developed by a clinical pharmacy team at an Egyptian ICU. Physicians were provided with educational sessions, information regarding the protocol, and latest SUP guidelines over a 1-month period. All adult patients admitted to one of the two ICU floors during the 6-month study period were eligible for inclusion. Patients admitted with an indication for acid suppressive therapy and those who stayed in the ICU for < 48 h were excluded. Patients were divided into two groups based on their ICU floor: PhyEd (1st floor) and PhyEd + CPh (2nd floor). Clinical pharmacists provided interventions regarding protocol adherence only for patients on the 2nd floor.

Results A total of 177 patients were included. SUP protocol non-adherence, calculated as the percentage of inappropriate (i.e., did not meet all the criteria in the protocol) patient-days, was significantly lower in the PhyEd + CPh group than in the PhyEd group (64.7% vs 90.9%; $p < 0.0001$). Bleeding events were comparable in both groups. The total actual cost saved due to protocol adherence was $US149.44 ($US118.95 in the PhyEd + CPh group + $US30.49 in the PhyEd group). The estimated total cost saved due to protocol adherence was $US948.56.

Conclusion Clinical pharmacists' daily interventions decreased non-adherence to the SUP protocol, and provided a significant decrease in hospital expenditures with no influence on adverse effects.

Introduction

Stress gastropathy in the intensive care unit (ICU) occurs due to hypoperfusion to mucosal cells and impaired mucosal repair mechanisms that can result in stress-related mucosal bleeding (SRMB) [1]. A landmark trial reported that the prevalence of SRMB in patients admitted to ICUs was 1.5% with the use of stress ulcer prophylaxis (SUP) [2]. Accordingly, SUP using acid suppression therapies (ASTs) became the standard of practice in ICUs for many years to decrease the morbidity and mortality associated with SRMB [3, 4]. However, the incidence of SRMB has declined with advances in the resuscitation and management of critically ill patients, maintenance of adequate systemic perfusion, and initiation of early enteral nutrition [5–8]. Current guidelines recommend AST only for patients at high risk of upper gastrointestinal (GI) bleeding [4, 9–11].

Proton pump inhibitors (PPIs) and histamine H_2-receptor antagonists (H2RAs) are the two recommended ASTs for SUP. According to a recent systematic

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✉ Naglaa Samir Bazan
naglaabazan@cu.edu.eg

Samar Farghali Farid
samar.farid@pharma.cu.edu.eg

Darrin Lloyd Baines
dbaines@bournemouth.ac.uk

1 Clinical Pharmacy, Critical Care Medicine Department, Cairo University Hospitals, Kasr Alini Street, Cairo, Egypt

2 Pharmacy Practice and Clinical Pharmacy Department, Faculty of Pharmacy, Future University in Egypt, Cairo, Egypt

3 Clinical Pharmacy Department, College of Pharmacy, Cairo University, Cairo, Egypt

4 Health Economics, Department of Accounting, Finance and Economics, Bournemouth University, Bournemouth, England

review and network meta-analysis, PPIs and H2RAs likely result in important reductions in GI bleeding compared with no prophylaxis in higher risk, critically ill patients only, and reductions in bleeding may be unimportant in low-risk patients [12]. However, up to 70% of patients admitted to hospital receive SUP without an appropriate indication. Inappropriate prescribing of these agents for SUP is associated with potential adverse effects and drug interactions, as well as additional healthcare costs [4]. Patients receiving SUP are at increased risk of both community and nosocomial pneumonia, myocardial infarction, osteoporosis, and *Clostridium difficile* infection (CDI) [8, 13–17].

In order to minimize inappropriate prescribing of ASTs in the ICU setting, it is essential to identify critically ill patients eligible for SUP using guidelines and protocols [18, 19]. However, guidelines are still not being adequately implemented in actual clinical practice [20–22], and simply providing clinicians with SUP protocols based on the presence of risk factors does not necessarily lead to a change in clinical practice [23–26].

Clinical pharmacists are experts in the therapeutic use of medications, with their contributions to patient care, improved pharmacotherapy outcomes, and savings being well documented [27, 28]. Pharmacists can promote appropriate SUP by developing and implementing treatment protocols and educational programs based on the best available evidence. In the ICU in particular, pharmacists often are members of the primary-care team; however, the impact of clinical pharmacists in providing education on SUP protocols to physicians compared with daily participation of pharmacists in implementing those protocols in addition to providing education has not been previously addressed, to the best of our knowledge, in Egypt or elsewhere.

This study was designed to evaluate the impact and possible cost saving of pharmacists providing physician education (PhyEd) alone versus PhyEd + daily clinical pharmacists interventions (PhyEd + CPh) on adherence to the SUP protocol in critically ill patients in the ICU.

Methods

This was a prospective, non-randomized, quasi-experimental study. Patients were recruited from those admitted to the two floors of the Critical Care Medicine Centre (CCMC) at Cairo University Hospital from July 1, 2017 to December 31, 2017. All adult patients admitted during the 6-month period were screened; patients admitted with an indication for AST and those who stayed in the ICU for < 48 h were excluded. All readmitted patients were considered new patients (Fig. 1).

Protocol development and patient allocation

The clinical pharmacy team at the CCMC performed a comprehensive literature search and developed an evidence-based prescribing protocol to promote appropriate prescribing of SUP (Appendix 1, see electronic supplementary material [ESM]). The protocol was approved by the Council of Critical Care Medicine Department, Faculty of Medicine, Cairo University. Mechanical ventilation and/or coagulopathy were considered independent risk factors for SUP. Dual antiplatelet therapy was considered an indication for oral PPIs. Based on latest evidence and due to controversies in the literature, it was agreed to consider H2RAs and PPIs to have similar efficacy and safety [4, 9, 10, 29–32].

Clinical pharmacists provided physicians who worked in critical care with educational sessions and information regarding the protocol and latest evidence of SUP guidelines over a 1-month period. Further education was provided in small group sessions whenever possible for new residents who arrived during the study period. Patients were divided into two groups based on the CCMC floor to which they were admitted: the PhyEd group comprised patients on the first floor of the CCMC, where no clinical pharmacists were available to perform clinical activities, and the PhyEd + CPh group comprised patients on the second floor, where clinical pharmacists performed comprehensive medical file reviews, revised prescriptions daily for adherence to the SUP protocol, attended medical rounds, and provided recommendations when the protocol was violated. Patient allocation to either first or second floor was based on bed availability at time of admission and the occupancy rate of the two floors. All participants (physicians, clinical pharmacists, and patients) were aware of the patients' groups.

Patients' demographics, concurrent medications, kidney and liver function tests, and complete blood counts were documented at baseline and followed-up during the study period. GI bleeding in the form of hematemesis and/or melena occurring during the study period was recorded.

Primary outcomes

Protocol non-adherence was calculated as percentage of inappropriate (i.e., did not meet all the criteria in the protocol) patient-days over the admission period. Evaluation of protocol ended if patients experienced GI hemorrhage requiring PPI infusion for 72 h and/or endoscopy. Protocol non-adherence in the two groups was assessed according to four criteria: non-adherence to agent choice, inappropriate indication, dose, and route of administration [28].

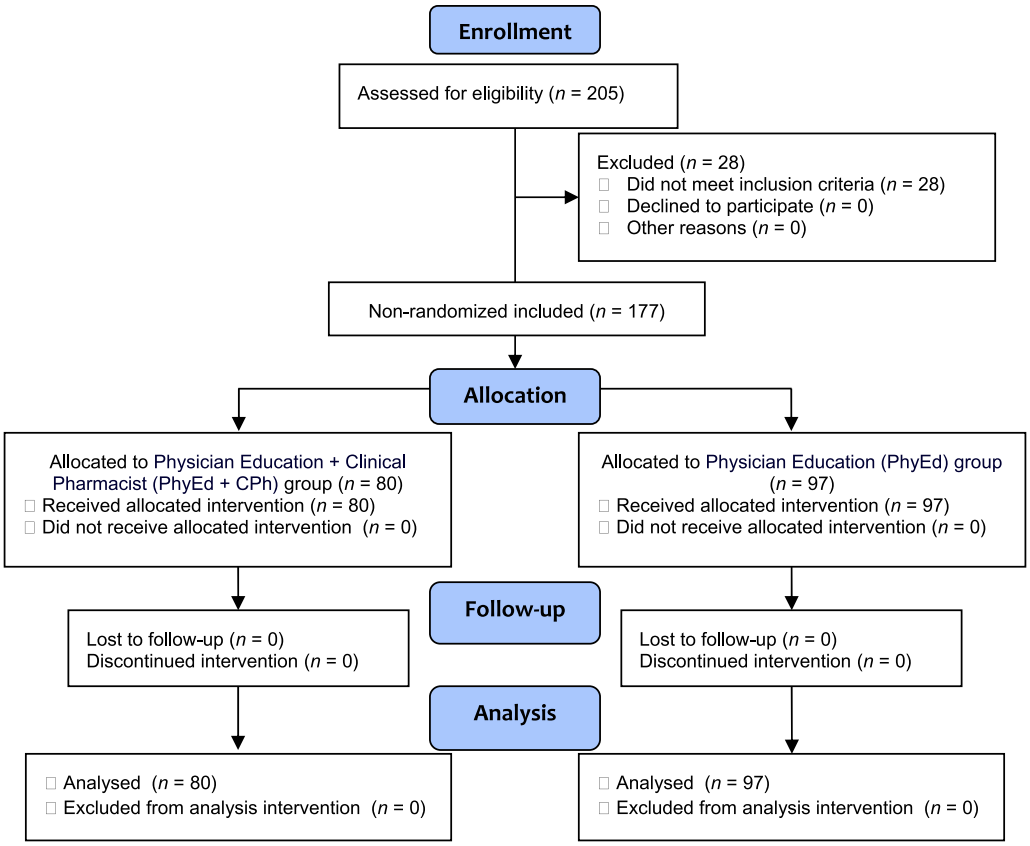
Enrollment
Assessed for eligibility (n = 205)
Excluded (n = 28)
Did not meet inclusion criteria (n = 28)
Declined to participate (n = 0)
Other reasons (n = 0)
Non-randomized included (n = 177)
Allocation
Allocated to Physician Education + Clinical Pharmacist (PhyEd + CPh) group (n = 80)
Received allocated intervention (n = 80)
Did not receive allocated intervention (n = 0)
Allocated to Physician Education (PhyEd) group (n = 97)
Received allocated intervention (n = 97)
Did not receive allocated intervention (n = 0)
Follow-up
Lost to follow-up (n = 0)
Discontinued intervention (n = 0)
Lost to follow-up (n = 0)
Discontinued intervention (n = 0)
Analysis
Analysed (n = 80)
Excluded from analysis intervention (n = 0)
Analysed (n = 97)
Excluded from analysis intervention (n = 0)

Fig. 1 Flow diagram for the non-randomized study

Inappropriate indication for SUP was defined as absence of at least one independent risk factor and/or two or more minor risk factors (Appendix 1, ESM). Non-adherence was calculated as percentage of total days patients were eligible for assessment by SUP protocol, and was confirmed if the regimen did not meet all four criteria. For patients who did not receive prophylaxis, only the criterion related to the indication was evaluated. Length of appropriate and inappropriate SUP in days was calculated in the two groups. Non-appropriateness of SUP prescribing was assessed through ICU length of stay (LOS) and at the time of transfer from the ICU.

Economic outcomes were measured by PPI and H2RA drug costs directly related to SUP, and were converted to US dollars ($US). In 2017, the year of the study, the average exchange rate of the Egyptian pound (LE) to the $US was $US0.0561 [33]. The daily cost for administering each drug in the protocol was 18.5 LE ($US1.04) for intravenous (IV) pantoprazole; 2.6 LE ($US0.15) for thrice daily ranitidine IV; 1 LE ($US0.056) for twice-daily omeprazole 20 mg capsules; and 0.7 LE ($US0.039) for twice-daily ranitidine 150 mg tablets. The cost of IV drugs included the price of the syringes used in administration. The cost per patient was based on the purchase cost of the drug by the hospital at time of the study multiplied by the number of doses received. Nursing time required for administering the drug was not included, as evaluation of these costs exceeded the objectives of our study. Both actual cost saved due to protocol adherence, and estimated cost saving if protocol adherence was 100%, were calculated.

Secondary outcomes

Secondary outcomes included the incidence of clinically significant GI bleeding (i.e., bleeding requiring treatment with continuous IV infusion of pantoprazole, blood transfusion, surgery, or according to the clinical judgment of the physician), ICU LOS, and mortality. The appropriateness of continuation of AST on patients' discharge or transfer to the ward (i.e., when the patient's physiologic status had stabilized and ICU monitoring and treatment were no longer required) [34] was also assessed.

Statistical analysis

Data management and analysis were performed using the Statistical Software Package for Social Sciences (SPSS) version 22 and graphics utilizing Microsoft Excel 2010. All continuous data were expressed as means ± standard deviation (SD), and were compared using the Student's *t* test as per non-significant Shapiro Wilk tests ($p > 0.05$), while non-normally distributed variables (as per significant Shapiro Wilk tests ($p < 0.05$) were compared using the Mann Whitney *U* test. Categorical variables were compared using χ^2 tests, and were reported as count (%). *P* values of ≤ 0.05 were considered statistically significant.

Sample size calculation and sample power

Sample size and power were calculated using G Power 3.1.9.4 software. Post-hoc analysis was performed using the percentage of patient days of protocol non-adherence (90.9% in the PhyEd group vs 64.7% in the PhyEd + CPh group), α error probability = 5%. The calculated power was 99% with actual $\alpha = 0.036$. When using the results obtained from a study published in 2018 (incidence of inappropriate SUPs 26.75 and 7.14 per 100 patient-days in the pre- and post-interventional phases, respectively) [35], the computed total sample size was 166 patients, assuming that α error probability = 5% and the power is 95%.

Results

A total of 205 patients were evaluated, of whom 177 patients met the inclusion criteria and were enrolled in one of two groups: PhyEd ($n = 97$) and PhyEd + CPh ($n = 80$). Patient demographics and clinical characteristics are shown in Table 1.

Clinical outcomes during intensive care unit stay

The protocol was applied for a total of 1741 of the 1811 ICU LOS days (781/818 ICU LOS days in PhyEd group vs 960/993 ICU LOS in PhyEd + CPh group).The percentage of days patients received SUP inappropriately due to protocol non-adherence was slightly lower in the PhyEd + CPh group (64.7%; 621/960 days) than in the PhyEd group (90.9%; 710/781 days) with a relative risk reduction [RRR] of 28.8% ($p < 0.0001$, Fig. 2). Moreover, PhyEd + CPh significantly increased the mean number of days on protocol versus PhyEd. The incidence of clinically significant GI bleeding was comparable in the two groups (Table 2).

Table 1 Demographic and clinical characteristics of the study groups

Parameter	PhyEd ($n = 97$)	PhyEd + CPh ($n = 80$)	*p*-value
Age in years, mean ± SD	58.3 ± 17.6	54.8 ± 19	0.201[a]
Male, no. of pts (%)	54 (55.7)	34 (42.5)	0.081[b]
Acute kidney injury, no. of pts (%)	5 (5.2)	13 (16.2)	0.015[b]
Sepsis, no. of pts (%)	10 (10.3)	11 (13.8)	0.481[b]
ICU stay > 1 wk, no. of pts (%)	30 (30.9)	43 (53.8)	0.002[b]
Mechanical ventilation > 48 h, no. of pts (%)	26 (26.8)	28 (35)	0.239[b]
Coagulopathy, no. of pts (%)	9 (9.3)	5 (6.2)	0.458[b]
At least 1 independent risk factor, no. of pts (%)	30 (30.9)	31 (38.8)	0.226[b]
Eligible for oral therapy, no. of pts (%)	76 (78.4)	61 (76.2)	0.739[b]
Risk factors, mean ± SD	2.53 ± 1.58	3.12 ± 1.78	0.021[a]
≥ 2 minor risk factors, no. of pts (%)	41 (42.3)	36 (45)	0.226[b]
Initial proton pump inhibitor, no. of pts (%)	71 (73.2)	78 (97.5)	0.0001[b]
Medications, no. of pts (%)			
Aspirin 75 mg	60 (61.9)	39 (48.9)	0.08[b]
Clopidogrel 75 mg	41 (42.3)	16 (20)	0.002[b]
Dual antiplatelet therapy	36 (37.1)	15 (18.8)	0.007[b]
Anticoagulants	87 (89.7)	72 (90)	0.946[b]
Corticosteroids (equivalent to > 250 mg of hydrocortisone)	17 (17.5)	34 (42.5)	0.0001[b]

ICU intensive care unit, *PhyEd* physician education, *PhyEd + CPh* PhyEd + clinical pharmacist, *pts* patients, *SD* standard deviation

[a]Independent Student's *t* test

[b]χ^2 test

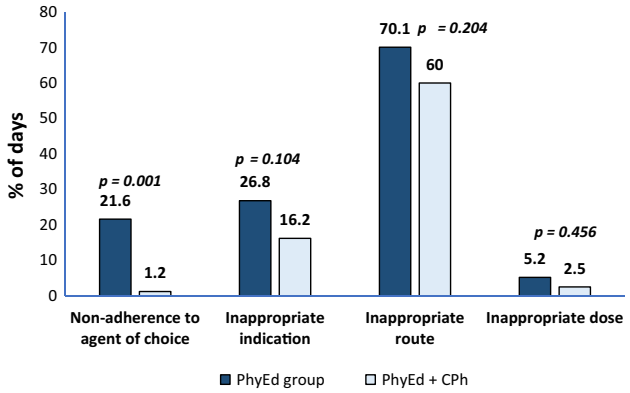

Fig. 2 Percentage of days of non-adherence for each of the four protocol criteria

Clinical outcomes at discharge or transfer

A total of 138 patients survived to discharge or ICU transfer during the study period (77 in PhyEd group vs 61 in PhyEd + CPh group). A total of 88 patients (63.7%) had their SUP continued inappropriately on discharge or ICU transfer; 43 (55.8%) in the PhyEd group versus 45 patients (73.8%) in the PhyEd + CPh group ($p = 0.034$).

Cost analysis

The actual cost saved due to protocol adherence in the two groups was $US149 ($US30 + $US119 in the PhyEd + PhyEd + CPh groups, respectively. The total cost of days of protocol adherence was $US274 whereas the cost of days of protocol non-adherence was $US1013. The total cost at the hospital was $US1287 ($US507 + $US780 in the PhyEd + PhyEd + CPh groups), whereas the total cost if protocol adherence was 100% would have been $US339 ($US128 + $US210 in the PhyEd and PhyEd + CPh groups) with an estimated total cost saved of $US949 ($US379 + $US570 in the PhyEd + PhyEd + CPh groups; Table 3).

Table 2 Clinical outcomes of the protocol during ICU stay in the study groups

Outcome	PhyEd ($n = 97$)	PhyEd + CPh ($n = 80$)	p-value
Days of protocol adherence, mean ± SD	0.73 ± 2.03	4.2 ± 12.2	0.01[a]
Days of protocol non-adherence, mean ± SD	7.31 ± 10.07	7.76 ± 11.56	0.54[a]
Conversion to oral therapy, no. of pts (%)	7 (7.2)	13 (16.2)	0.059[b]
Gastrointestinal hemorrhage, no. of pts (%)	7 (7.2)	8 (10)	0.508[b]
Mortality, no. of pts (%)	20 (20.6)	19 (23.8)	0.617[b]
Length of ICU stay, mean no. of days ± SD	8.43 ± 10.5	12.4 ± 15.01	0.007[b]

ICU intensive care unit, *PhyEd* physician education, *PhyEd + CPh* PhyEd + clinical pharmacist, *pts* patients, *SD* standard deviation

[a]Mann Whitney *U* test

[b]χ^2 test

Table 3 Comparison of protocol costs during ICU stay in the study groups

Parameter	Cost ($US; year of costing 2017)		
	PhyEd ($n = 97$)	PhyEd + CPh ($n = 80$)	Total
Actual total cost[a]	507	780	1287
Estimated total cost if protocol adherence was 100%[b]	128	210	339
Actual total cost saved due to protocol adherence[c]	30	119	149
Estimated cost saved if protocol adherence was 100%[d]	379	570	949

ICU intensive care unit, *PhyEd* physician education, *PhyEd + CPh* PhyEd + clinical pharmacist, *SD* standard deviation

[a]Cost of drug in 2017 multiplied by number of daily doses taken during the study period

[b]Cost of drug multiplied by the number of doses that should have taken if protocol adherence was 100% during the study period

[c]Equals estimated cost if protocol was not used minus the actual cost (a)

[d]Equals actual cost (a) minus the estimated total cost for 100% protocol adherence (b)

Discussion

Recent evidence suggests that the use of SUP to prevent SRMB must be balanced against the risk of pneumonia, CDI, and increased healthcare costs [12, 36]. Few studies showed that targeted educational interventions on appropriateness of SUP in critically ill adults and pharmacist-driven SUP protocols led to a reduction in overall drug costs without increasing the risk of adverse effects [23–26, 37]. However, based on our knowledge, no studies to date prospectively compared the adherence of prescribers to an SUP protocol and its cost savings by using educational sessions only versus both education and clinical pharmacist-driven interventions in critically ill patients. Most other studies were 'pre' versus 'post' studies, whereas our study had a non-randomized, prospective,quasi-experimental design, and evaluated the impact of providing PhyEd alone versus PhyEd + CPh on adherence to an SUP protocol and cost savings in critically ill patients. PhyEd + CPh reduced the percentage of days patients received SUP inappropriately due to protocol non-adherence by 28.8% relative to PhyEd alone (64.7% vs 90.9%; $p < 0.0001$). Moreover, the addition of clinical pharmacists interventions to PhyEd significantly increased the mean number of days of protocol adherence relative to PhyEd alone (4.2 vs 0.73 days; $p = 0.01$).

A study conducted in the ICU of a Canadian hospital evaluated the impact of a treatment algorithm introduced by pharmacists on the appropriateness of prescriptions for SUP versus pre-interventional phase. After implementation of the algorithm, the proportion of patients receiving inappropriate prophylaxis decreased (95.7% vs 88.2%; $p = 0.033$) [25]. The lower relative reduction in inappropriate prophylaxis relative to our study may be because they used an omeprazole suspension that included sodium bicarbonate, which was not accepted by critical care physicians, whereas we used omeprazole capsules. Moreover, the latter study was conducted for only a 2-month period [25], whereas we evaluated the outcome to protocol adherence after 6 months. Accordingly, it is possible that the physicians did not have sufficient experience with the proposed guidelines and that a more prolonged study may have led to sustained or better results.

In our study, days of protocol adherence differed significantly between the PhyEd and PhyEd + CPh groups [71 (9.1%) vs 339 days (35.3%); $p < 0.0001$]. However, in a Brazilian prospective cohort study, adherence to the SUP protocol in critically ill patients at a tertiary university hospital was much higher (73%) [38]. This higher adherence may be because our study protocol followed the American Society of Health-System Pharmacists (ASHP) guidelines, and mandated the use of SUP if one independent risk factor (e.g., mechanical ventilation and/or coagulopathy) or at least two dependent factors were present [4]. However, the Brazilian study considered the presence of some of the dependent factors, chronic liver disease with cirrhosis and therapeutic anticoagulant use, as an indication for SUP [38]. Secondly, our study considered AST administration via IV in patients eligible for oral administration as a criteria for non-adherence to the SUP protocol.

A retrospective, observational, pre- and post-implementation study conducted in the USA evaluated a pharmacist-based quality initiative using ASHP guidelines as a reference to reduce inappropriate SUP use in an academic medical ICU [35]. The 1-month pre-implementation phase included chart review for all patients over 1 month to determine baseline SUP utilization. The 1-month post-implementation phase included pharmacists reviewing indications for SUP for each patient during daily rounds, and providing education on a bimonthly basis to residents rotating on ICU services. Pharmacist interventions were able to reduce inappropriate SUP usage to 7.14/100 patient-days (73.3% reduction; $p < 00.1$), and the total cost of inappropriate use to $US240 (2016 costing). However, unlike our study, oral administration in eligible patients was not a criteria for non-adherence [35]. Also, a study in Iran assessed all patients on the nephrology wards of a teaching hospital regarding appropriate SUP prescribing during a 6-month pre-intervention phase of the study without any clinical pharmacists' involvement. Thereafter, during a 6-month post-intervention phase, clinical pharmacists provided local SUP protocol and educational classes for physicians regarding appropriate SUP prescribing and participated actively in the patient care team. The results showed that clinical pharmacist interventions significantly reduced inappropriate SUP prescribing in patients with renal insufficiency by ≈ 44% [26]. Our results are also in accordance with two pre- versus post-intervention studies in the USA [23, 24]. In a retrospective, single-center ICU study, the rate of inappropriate SUP was significantly higher before implementation of a pharmacist-driven AST discontinuation protocol than after its implementation (61 vs 24 per 100 patient-days; $p < 0.0001$) [24]. Similarly, relative to without intervention, a structured educational intervention led by pharmacists on appropriateness of AST used for prevention of SRMB in an academic medical ICU significantly reduced the rate of inappropriate prescribing on the day of initiation from 23% to 11% [23]. We assume that this low rate of inappropriate prescribing relative to that in our study was due to their results being at initiation of therapy, whereas ours were throughout the whole ICU LOS. Moreover, the higher rate of inappropriate prescribing in our study may be attributed to the fact that one of the conditions of inappropriate prescribing included in the protocol was the appropriate route, which was not considered in most studies, which focused on inappropriate indications only. If we focused only on inappropriate indication of AST, the rates of inappropriate AST prescribing would be 26.8% in the PhyEd group versus 16.2% in the PhyEd + CPh group, which

are better in the PhyEd + CPh and comparable in the PhyEd group to the results in several studies that assessed the pattern of prescribing of SUP based on indication using the ASHP guidelines as reference [39–42].

In our study, on discharge or ICU transfer, AST was unnecessarily prescribed in significantly more patients in the PhyEd + CPh group than in the PhyEd group (73.8% vs 55.8%; $p = 0.034$), which may be attributed to significantly more patients in the PhyEd group than in the PhyEd + CPh group receiving dual antiplatelet therapy, which mandated the prescribing of PPIs on discharge [29]. In the Iranian study, 81.2% of the ICU patients continued to receive inappropriate prophylaxis upon transfer from the ICU [40]. Also, continuation of inappropriate AST at ICU transfer and hospital discharge was similar between pharmacist interventional and non-interventional groups (60% vs 53%; $p = 0.277$ and 18% vs 14%; $p = 0.368$, respectively) in the study [23]. Other studies conducted in the USA demonstrated similar findings [43–46], which highlights the need to implement solutions to decrease inappropriate prescribing at discharge. However, it is worth mentioning that studies that showed significant decreases in patients inappropriately discharged on AST from the ICU had pharmacists involved in reviewing and performing medication reconciliation on predischarge medications, and were allowed to discontinue any AST that lacked an appropriate indication pursuant to a protocol [47, 48]. Although this service was not implemented at our institution during the study period, it is now provided.

In our study, mortality rates were comparable in the two groups; however, the PhyEd + CPh group had a significantly longer ICU LOS, which could be explained by the higher total number of risk factors in the PhyEd + CPh group than in the PhyEd group.

Regarding GI bleeding events, no significant difference occurred between the PhyEd + CPh and PhyEd groups (7.2% and 10.0%). This is in accordance with other studies, which reported that adverse events occurred infrequently in both pharmacist interventional and non-interventional groups [23]; clinically important GI bleeding did not occur in either the pre- or post-implementation of the pharmacist-driven protocol groups; and there were no between-group differences in rates of nosocomial pneumonia or CDI [24]. Also, in a retrospective pre–post study at a single-center tertiary ICU, the incidence of upper GI bleeding was 4.0% both before and after setting administration criteria for SUP and introducing a medical checklist for critically ill adults [49].

In our study, the actual cost saving in 6 months due to protocol adherence was $US149 and estimated cost saved if protocol adherence was 100% was $US379 in the PhyEd group and $US570 in the PhyEd + CPh group. Of note, these cost savings were mainly based on protocol recommendations to switch from IV to oral AST in most patients. In the Kaifer and Grant study, estimated inappropriate drug cost was $US1142.49 in the pre-protocol arm compared with $US231 in the post-protocol arm with an estimated annualized cost savings of $US5496 [24]. Also, in the study on role of clinical pharmacist in appropriate SUP in patients with renal insufficiency, inappropriate SUP-related costs decreased by ≈ 67% with pharmacist intervention [26].

Our study made no distinction with regard to the efficacy and safety of the two AST classes, since evidence is controversial regarding their comparative effectiveness in preventing upper GI bleeding in ICU patients [36, 50, 51]. Accordingly, they were used interchangeably, except when dual antiplatelet therapy was prescribed where PPIs were recommended [52]. In the PEPTIC randomized trial, there was no significant difference in in-hospital mortality rates between ICU patients receiving invasive mechanical ventilation using PPIs and those receiving H2RBs for SUP. Our study interpretation may be limited by crossover in the use of the assigned medication [53]. On the other hand, a recently published clinical practice guideline for GI bleeding prophylaxis in critically ill patients made a weak recommendation of using a PPI rather than an H2RA in this population, and strongly recommends against using sucralfate. The guideline also made weak recommendations for using GI bleeding prophylaxis in critically ill patients at high risk (> 4%) of clinically important GI bleeding, but not in those at lower risk (≤ 4%) [11].

Limitations

Our study was limited by its non-randomized study design from a single university hospital. Due to a shortage of pharmacy staff at the two-floor ICU during the study period, clinical pharmacists were occupied with dispensing activities and were asked by the administration to provide their daily clinical activities (i.e., comprehensive medical file review, attending physicians' rounds and providing recommendations) to patients on the second floor only. In order to assess the impact of physicians on adherence to SUP protocol without the daily influence of the clinical pharmacists and to prove the importance of daily clinical activities of clinical pharmacists, the authors decided to prospectively compare the service provided on the first and second floors. Accordingly, randomization might have led to performance bias (i.e., systematic differences in the care provided apart from the intervention being evaluated) [37, 38], since not all patients in the two groups would have had similar provision of daily clinical pharmacy activities. We also had no way to determine if patients developed an adverse effect, such as pneumonia or CDI, soon after hospital discharge, and likely underestimated the true incidence of these adverse events. Moreover, we assume that adherence to the protocol in the PhyEd + CPh group was affected by pharmacists being available only for 6 h/day on weekdays and not all on weekends.

Conclusion

Clinical pharmacists can play a crucial role in preventing misuse of AST and providing cost savings through decreasing non-adherence to SUP protocols in the ICU. As the route of administration represented the most common cause of protocol non-adherence, incorporating inappropriate route of administration as one of the criteria in the SUP protocol can contribute significantly to cost saving with no influence on adverse effects. Further studies are recommended to assess the effect of availability of clinical pharmacy services 24 h/day and/or developing drug control policies, such as formulary restriction, stop-orders for specific indications, and an automatic switch-order to oral PPI if patient is receiving oral feeding, on adherence to appropriate SUP and subsequent cost savings. In addition, strategies such as medication reconciliation and counseling services need to be implemented and evaluated for their role in decreasing inappropriate SUP continuation on discharge and/or ICU transfer.

Take-home messages

- Clinical pharmacists have a vital role in the implementation of, and adherence to, treatment protocols in critically ill patients.
- Cost savings are associated with adherence to stress ulcer prophylaxis (SUP) protocols, including the compulsory use of oral acid suppression therapy (AST) in eligible patients in the intensive care unit.
- As only high-risk, critically ill patients need SUP, individualized risk–benefit assessment through a standardized protocol is important to assess bleeding risk versus risk of adverse effects from AST.

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Declarations

Author contributions All authors were involved in the concept and design. NS Bazan collected the study data, performed the statistical analysis, interpreted the data, and wrote the first draft of the manuscript. All authors contributed to, and approved, the subsequent drafts.

Availability of data and materials The datasets generated during and/or analyzed during the current study are available from the corresponding author on request.

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Conflicts of interest Naglaa Samir Bazan, Samar Farghali Farid, and Darrin Lloyd Baines declare that they have no conflicts of interest.

Ethical approval Granted by the Research Ethics Committee at Faculty of Pharmacy, Cairo University, CL (2293).

Consent for participation/publication Consent was obtained from all participants.

Code availability Not applicable.

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